

This listing of claims replaces all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (currently amended) A method of treating acne in a human in need thereof comprising administering ~~systemically~~ orally or intravenously to said human a tetracycline compound in ~~an~~ a sub-antibacterial amount that reduces lesion count ~~is effective to treat acne~~ but has substantially no antibiotic activity, without administering a bisphosphonate compound.

2. (original) A method according to Claim 1, wherein said acne is acne vulgaris, cystic acne, acne atrophica, bromide acne, chlorine acne, acne conglobata, acne cosmetica, acne detergentica, epidemic acne, acne estivalis, acne fulminans, halogen acne, acne indurata, iodide acne, acne keloid, acne mechanica, acne papulosa, pomade acne, premenstrual acne, acne pustulosa, acne rosacea, acne scorbutica, acne scrofulosorum, acne urticata, acne varioliformis, acne venenata, propionic acne, acne excoriee, gram negative acne, steroid acne, or nodulocystic acne.

Claims 3-22 (cancelled).

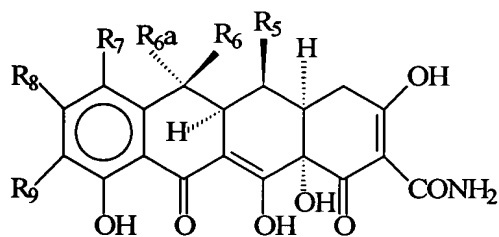
23. (original) A method according to Claim 1, wherein said tetracycline compound is a non-antibiotic tetracycline compound.

24. (original) A method according to Claim 23, wherein said non-antibiotic tetracycline compound is:

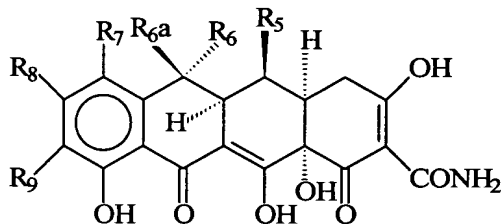
4-de(dimethylamino)tetracycline (CMT-1),
tetracyclonitrile (CMT-2),
6-demethyl-6-deoxy-4-de(dimethylamino)tetracycline (CMT-3),
4-de(dimethylamino)-7-chlorotetracycline (CMT-4),
tetracycline pyrazole (CMT-5)

4-hydroxy-4-de(dimethylamino)tetracycline (CMT-6),
4-de(dimethylamino)-12 α -deoxytetracycline (CMT-7),
6- α -deoxy-5-hydroxy-4-de(dimethylamino)tetracycline (CMT-8),
4-de(dimethylamino)-12 α -deoxyanhydrotetracycline (CMT-9), or
4-de(dimethylamino)minocycline (CMT-10).

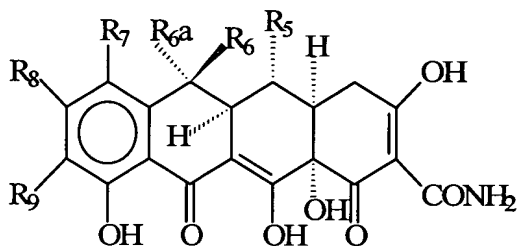
25. (original) A method according to Claim 23, wherein the non-antibiotic tetracycline compound is selected from the group consisting of:



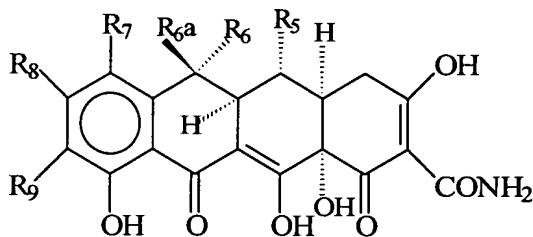
Structure C



Structure D



Structure E



Structure F

wherein:

R7 is selected from the group consisting of hydrogen, amino, nitro, mono(lower alkyl) amino, halogen, di(lower alkyl)amino, ethoxythiocarbonylthio, azido, acylamino, diazonium, cyano, and hydroxyl;

R6-a is selected from the group consisting of hydrogen and methyl;

R6 and R5 are selected from the group consisting of hydrogen and hydroxyl;

R8 is selected from the group consisting of hydrogen and halogen;

R9 is selected from the group consisting of hydrogen, amino, azido, nitro, acylamino, hydroxy, ethoxythiocarbonylthio, mono(lower alkyl) amino, halogen, diazonium, di(lower alkyl)amino and $\text{RCH}(\text{NH}_2)\text{CO}$;

R is hydrogen or lower alkyl; and

pharmaceutically acceptable salts thereof; with the following provisos:

when either R7 and R9 are hydrogen then R8 must be halogen; and

when R6-a, R6, R5 and R9 are all hydrogen and R7 is hydrogen, amino, nitro, halogen, dimethylamino or diethylamino, then R8 must be halogen; and

when R6-a is methyl, R6 and R9 are both hydrogen, R5 is hydroxyl, and R7 is hydrogen, amino, nitro, halogen or diethylamino, then R8 is halogen; and

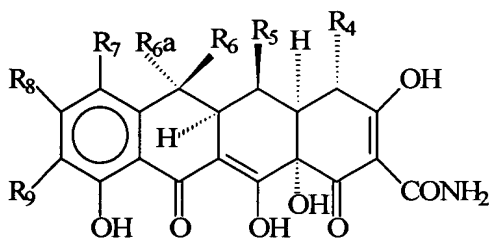
when R6-a is methyl, R6 is hydroxyl, R5, R7 and R9 are all hydrogen, then R8 must be halogen; and

when R6-a, R6 and R5 are all hydrogen, R9 is methylamino and R7 is dimethylamino, then R8 must be halogen; and

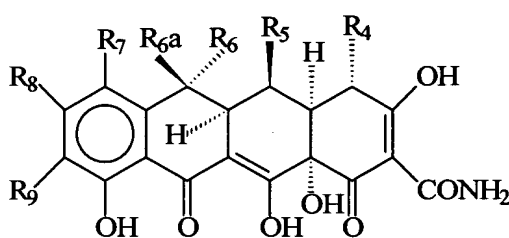
when R6-a is methyl, R6 is hydrogen, R5 is hydroxyl, R9 is methylamino and R7 is dimethylamino, then R8 must be halogen; and

when R6-a is methyl, R6, R5 and R9 are all hydrogen and R7 is cyano, then R8 must be halogen.

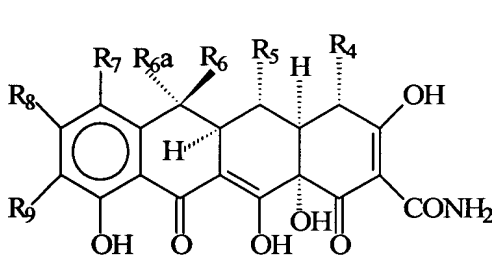
26. (original) A method according to Claim 23, wherein the non-antibiotic tetracycline compound is selected from the group consisting of:



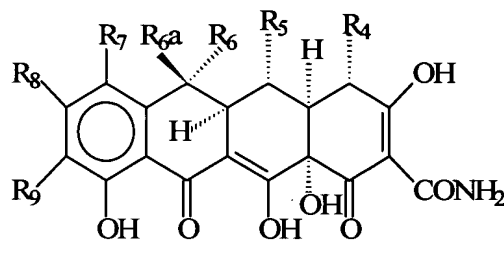
Structure G



Structure H



Structure I



Structure J

wherein:

R7 is selected from the group consisting of hydrogen, amino, nitro, mono(lower alkyl) amino, halogen, and di(lower alkyl)amino, ethoxythiocarbonylthio, azido, acylamino, diazonium, cyano, and hydroxyl;

R6-a is selected from the group consisting of hydrogen and methyl;

R6 and R5 are selected from the group consisting of hydrogen and hydroxyl;

R4 is selected from the group consisting of NOH, N-NH-A, and NH-A, where A is a lower alkyl group;

R8 is selected from the group consisting of hydrogen and halogen;

R9 is selected from the group consisting of hydrogen, amino, azido, nitro, acylamino, hydroxy, ethoxythiocarbonylthio, mono(lower alkyl) amino, halogen, di(lower alkyl)amino and RCH(NH₂)CO;

R is hydrogen or lower alkyl; and

pharmaceutically acceptable salts thereof; with the following provisos:

when R4 is NOH, N-NH-alkyl or NH-alkyl and R7, R6-a, R6, R5, and R9 are all hydrogen, then R8 must be halogen; and

when R4 is NOH, R6-a is methyl, R6 is hydrogen or hydroxyl, R7 is halogen, R5 and R9 are both hydrogen, then R8 must be halogen; and

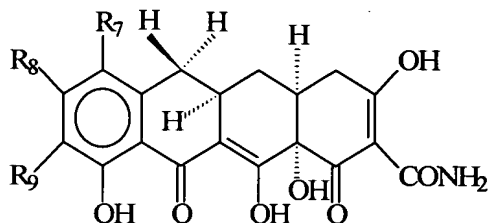
when R4 is N-NH-alkyl, R6-a is methyl, R6 is hydroxyl and R7, R5, R9 are all hydrogen, then R8 must be halogen; and

when R4 is NH-alkyl, R6-a, R6, R5 and R9 are all hydrogen, R7 is hydrogen, amino, mono(lower alkyl)amino, halogen, di(lower alkyl)amino or hydroxyl, then R8 must be halogen; and

when R4 is NH-alkyl, R6-a is methyl, R6 and R9 are both hydrogen, R5 is hydroxyl, and R7 is mono(lower alkyl)amino or di(lower alkyl)amino, then R8 must be halogen; and

when R4 is NH-alkyl, R6-a is methyl, R6 is hydroxy or hydrogen and R7, R5, and R9 are all be hydrogen, then R8 must be halogen.

27. (original) A method according to Claim 23 wherein the non-antibiotic tetracycline compound is selected from the group consisting of:



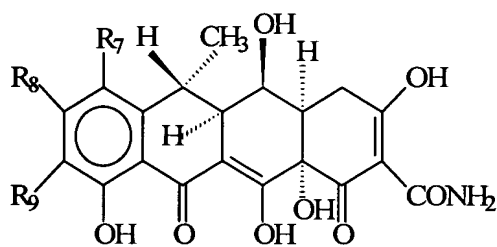
Structure K

wherein: R7, R8, and R9 taken together in each case, have the following meanings:

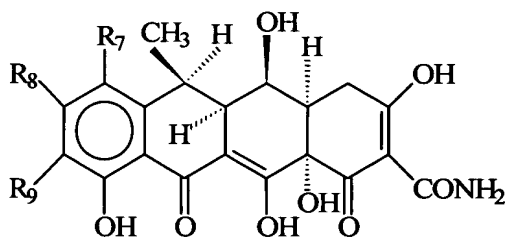
| R7 | R8 | R9 |
|---------------|----------|---------------------------|
| azido | hydrogen | hydrogen |
| dimethylamino | hydrogen | azido |
| hydrogen | hydrogen | amino |
| hydrogen | hydrogen | azido |
| hydrogen | hydrogen | nitro |
| dimethylamino | hydrogen | amino |
| acylamino | hydrogen | hydrogen |
| hydrogen | hydrogen | acylamino |
| amino | hydrogen | nitro |
| hydrogen | hydrogen | (N,N-dimethyl)glycylamino |
| amino | hydrogen | amino |

| | | |
|----------------|----------|------------------------|
| hydrogen | hydrogen | ethoxythiocarbonylthio |
| dimethylamino | hydrogen | acylamino |
| dimethylamino | hydrogen | diazonium |
| dimethylamino | chloro | amino |
| hydrogen | chloro | amino |
| amino | chloro | amino |
| acylamino | chloro | acylamino |
| amino | chloro | hydrogen |
| acylamino | chloro | hydrogen |
| monoalkylamino | chloro | amino |
| nitro | chloro | amino |
| dimethylamino | chloro | acylamino |
| dimethylamino | chloro | dimethylamino |
| hydrogen | hydrogen | dimethylamino |
| dimethylamino | hydrogen | hydrogen |

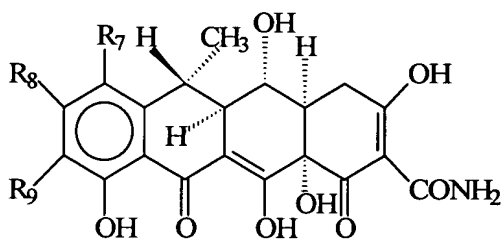
and



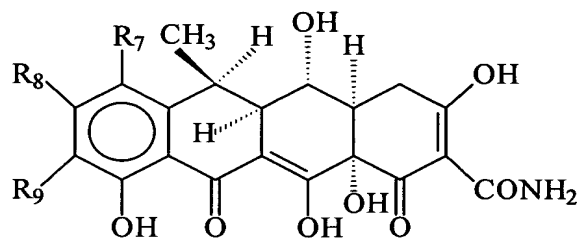
Structure L



Structure M



Structure N

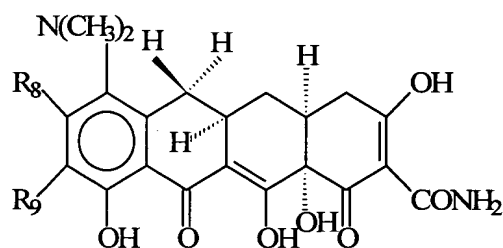


Structure O

wherein: R7, R8, and R9 taken together in each case, have the following meanings:

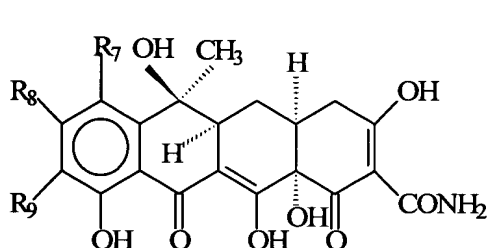
| R7 | R8 | R9 |
|------------------------|----------|---------------------------|
| azido | hydrogen | hydrogen |
| dimethylamino | hydrogen | azido |
| hydrogen | hydrogen | amino |
| hydrogen | hydrogen | azido |
| hydrogen | hydrogen | nitro |
| dimethylamino | hydrogen | amino |
| acylamino | hydrogen | hydrogen |
| hydrogen | hydrogen | acylamino |
| amino | hydrogen | nitro |
| hydrogen | hydrogen | (N,N-dimethyl)glycylamino |
| amino | hydrogen | amino |
| hydrogen | hydrogen | ethoxythiocarbonylthio |
| dimethylamino | hydrogen | acylamino |
| hydrogen | hydrogen | diazonium |
| hydrogen | hydrogen | dimethylamino |
| diazonium | hydrogen | hydrogen |
| ethoxythiocarbonylthio | hydrogen | hydrogen |
| dimethylamino | chloro | amino |
| amino | chloro | amino |
| acylamino | chloro | acylamino |
| hydrogen | chloro | amino |
| amino | chloro | hydrogen |
| acylamino | chloro | hydrogen |
| monoalkylamino | chloro | amino |
| nitro | chloro | amino |

and

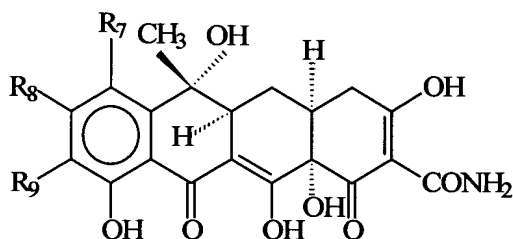


Structure P

wherein: R8 is hydrogen or halogen and R9 is selected from the group consisting of nitro, (N,N-dimethyl)glycylamino, and ethoxythiocarbonylthio; and



Structure Q



Structure R

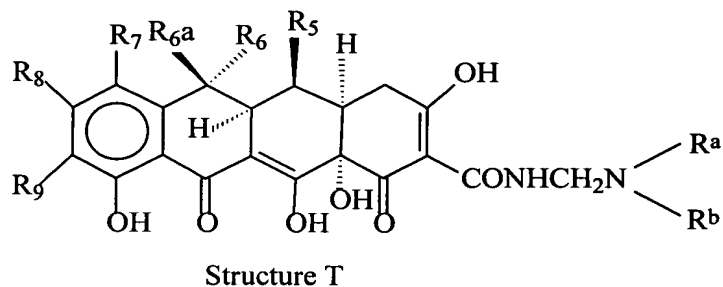
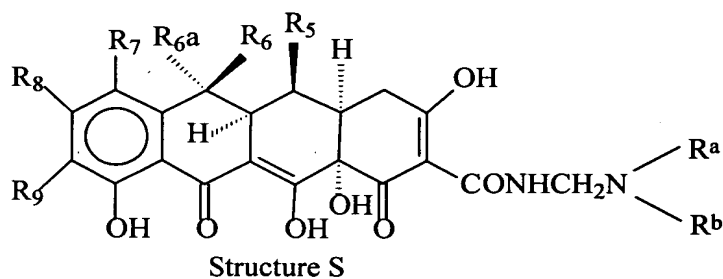
wherein: R7, R8, and R9 taken together in each case, have the following meanings:

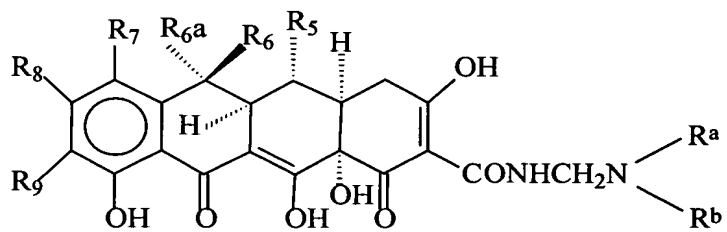
| R7 | R8 | R9 |
|---------------|----------|---------------------------|
| amino | hydrogen | hydrogen |
| nitro | hydrogen | hydrogen |
| azido | hydrogen | hydrogen |
| dimethylamino | hydrogen | azido |
| hydrogen | hydrogen | amino |
| hydrogen | hydrogen | azido |
| hydrogen | hydrogen | nitro |
| bromo | hydrogen | hydrogen |
| dimethylamino | hydrogen | amino |
| acylamino | hydrogen | hydrogen |
| hydrogen | hydrogen | acylamino |
| amino | hydrogen | nitro |
| hydrogen | hydrogen | (N,N-dimethyl)glycylamino |
| amino | hydrogen | amino |
| diethylamino | hydrogen | hydrogen |
| hydrogen | hydrogen | ethoxythiocarbonylthio |

| | | |
|----------------|----------|-------------|
| dimethylamino | hydrogen | methylamino |
| dimethylamino | hydrogen | acylamino |
| dimethylamino | chloro | amino |
| amino | chloro | amino |
| acylamino | chloro | acylamino |
| hydrogen | chloro | amino |
| amino | chloro | hydrogen |
| acylamino | chloro | hydrogen |
| monoalkylamino | chloro | amino |
| nitro | chloro | amino |

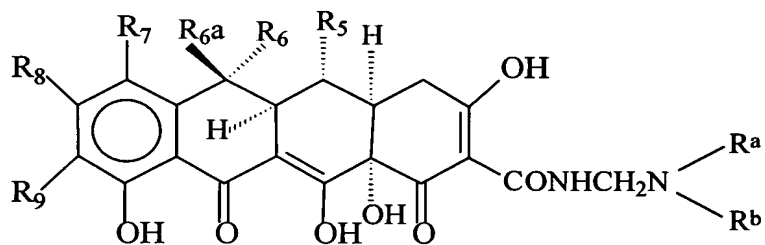
and pharmaceutically acceptable salts thereof.

28. (original) A method according to Claim 23, wherein the non-antibiotic tetracycline compound is selected from the group consisting of:

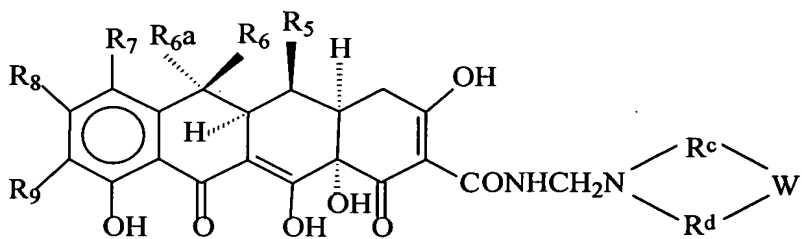




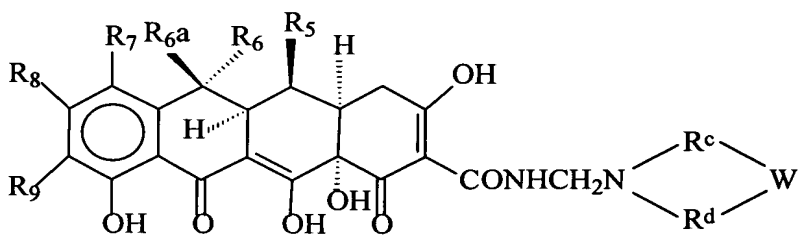
Structure U



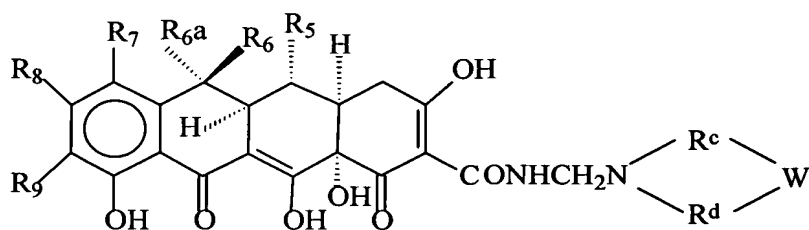
Structure V



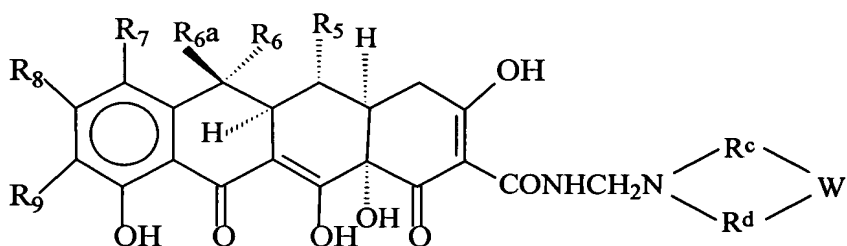
Structure W



Structure X



Structure Y



Structure Z

wherein:

R₇ is selected from the group consisting of hydrogen, amino, nitro, mono(lower alkyl) amino, halogen, di(lower alkyl)amino, ethoxythiocarbonylthio, azido, acylamino, diazonium, cyano, and hydroxyl;

R_{6-a} is selected from the group consisting of hydrogen and methyl;

R₆ and R₅ are selected from the group consisting of hydrogen and hydroxyl;

R₈ is selected from the group consisting of hydrogen and halogen;

R₉ is selected from the group consisting of hydrogen, amino, azido, nitro, acylamino, hydroxy, ethoxythiocarbonylthio, mono(lower alkyl) amino, halogen, diazonium, di(lower alkyl)amino and RCH(NH₂)CO;

R is hydrogen or lower alkyl;

R^a and R^b are selected from the group consisting of hydrogen, methyl, ethyl, n-propyl and 1-methylethyl with the proviso that R^a and R^b cannot both be hydrogen;

R^c and R^d are, independently, (CH₂)_nCHR^e wherein n is 0 or 1 and R^e is selected from the group consisting of hydrogen, alkyl, hydroxy, lower(C₁-C₃) alkoxy, amino, or nitro; and,

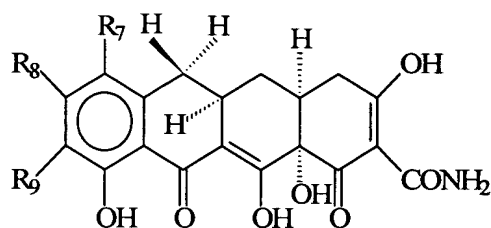
W is selected from the group consisting of $(\text{CHR}^e)_m$ wherein m is 0-3 and said R^e is as above, NH, $\text{N}(\text{C}_1\text{-C}_3)$ straight chained or branched alkyl, O, S and $\text{N}(\text{C}_1\text{-C}_4)$ straight chain or branched alkoxy; and,
pharmaceutically acceptable salts thereof.

29. (currently amended) A method according to Claim 23 ~~Claim 16~~, wherein the non-antibiotic tetracycline compound selected from the group consisting of structures S-Z has the following provisos:

- when either R7 and R9 are hydrogen then R8 must be halogen; and
- when R6-a, R6, R5 and R9 are all hydrogen and R7 is hydrogen, amino, nitro, halogen, dimethylamino or diethylamino, then R8 must be halogen; and
- when R6-a is methyl, R6 and R9 are both hydrogen, R5 is hydroxyl, and R7 is hydrogen, amino, nitro, halogen or diethylamino, then R8 is halogen; and
- when R6-a is methyl, R6 is hydroxyl, R5, R7 and R9 are all hydrogen, then R8 must be halogen; and
- when R6-a, R6 and R5 are all hydrogen, R9 is methylamino and R7 is dimethylamino, then R8 must be halogen; and
- when R6-a is methyl, R6 is hydrogen, R5 is hydroxyl, R9 is methylamino and R7 is dimethylamino, then R8 must be halogen; and
- when R6-a is methyl, R6, R5 and R9 are all hydrogen and R7 is cyano, then R8 must be halogen.

Claims 30 - 31 (cancelled).

32. (currently amended) A method according to Claim 23 ~~Claim 31~~, wherein said tetracycline compound has a general formula:

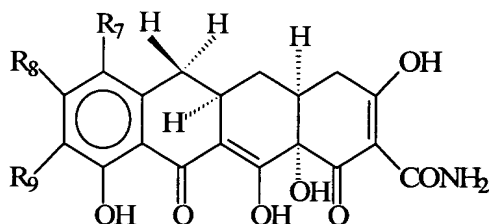


Structure K

wherein R7, R8, and R9 taken together are, respectively, hydrogen, hydrogen and dimethylamino.

Claim 33 (canceled).

34. (currently amended) A method according to Claim 23 ~~Claim 33~~, wherein said tetracycline compound is selected from the group consisting of:



Structure K

wherein R7, R8, and R9 taken together in each case, have the following meanings:

R7

R8

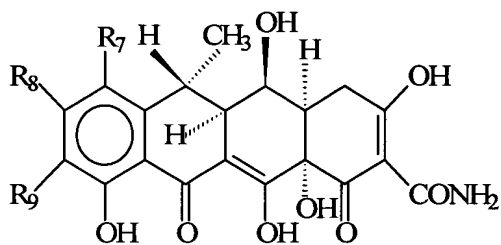
R9

hydrogen
hydrogen

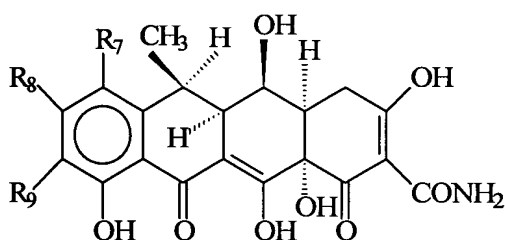
hydrogen
hydrogen

amino
palmitamide

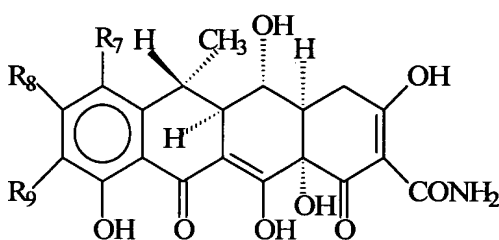
and



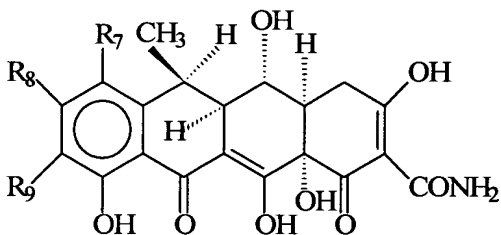
Structure L



Structure M



Structure N



Structure O

wherein R7, R8, and R9 taken together in each case, have the following meanings:

R7

hydrogen
 hydrogen
 hydrogen
 hydrogen

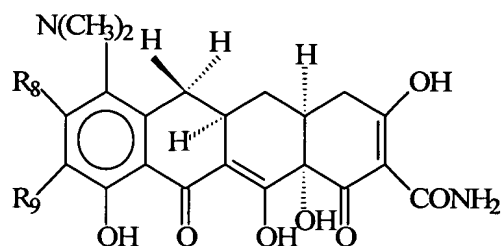
R8

hydrogen
 hydrogen
 hydrogen
 hydrogen

R9

acetamido
 dimethylaminoacetamido
 nitro
 amino

and



Structure P

wherein R₈, and R₉ taken together are, respectively, hydrogen and nitro.

Claim 35 (canceled).

36. (currently amended) A method of treating acne in a human in need thereof comprising administering to said human an effective amount of 6-demethyl-6-deoxy-4-de(dimethylamino)tetracycline ~~a non-antibiotic tetracycline compound~~ without administering a bisphosphonate compound.

Claim 37 (cancelled).

38. (original) A method according to Claim 36, wherein said administration is systemic administration.

Claims 39 - 45 (cancelled).

46. (new) A method according to Claim 1, wherein said tetracycline compound is an antibiotic tetracycline compound administered in an amount which is 10-80% of the antibiotic amount.

47. (new) A method according to Claim 1, wherein said tetracycline compound is doxycycline administered twice a day in a dose of 20 mg.

48. (new) A method according to Claim 1, wherein said tetracycline compound is minocycline administered once a day in a dose of 38 mg.

49. (new) A method according to Claim 1, wherein said tetracycline compound is minocycline administered twice a day in a dose of 38 mg.

50. (new) A method according to Claim 1, wherein said tetracycline compound is minocycline administered three times a day in a dose of 38 mg.

51. (new) A method according to Claim 1, wherein said tetracycline compound is minocycline administered four times a day in a dose of 38 mg.

52. (new) A method according to Claim 1, wherein said tetracycline compound is tetracycline administered once a day in a dose of 60 mg/day.

53. (new) A method according to Claim 1, wherein said tetracycline compound is tetracycline administered twice a day in a dose of 60 mg/day.

54. (new) A method according to Claim 1, wherein said tetracycline compound is tetracycline administered three times a day in a dose of 60 mg/day.

55. (new) A method according to Claim 1, wherein said tetracycline compound is tetracycline administered four times a day in a dose of 60 mg/day.

56. (new) A method according to Claim 1, wherein said tetracycline compound is an antibiotic tetracycline compound administered in an amount which results in a serum concentration which is 10-80% of the minimum antibiotic serum concentration.

57. (new) A method according to Claim 1, wherein said tetracycline compound is doxycycline administered in an amount which results in a serum concentration which is 1.0 µg/ml.

58. (new) A method according to Claim 1, wherein said tetracycline compound is minocycline administered in an amount which results in a serum concentration which is 0.8 µg/ml.

59. (new) A method according to Claim 1, wherein said tetracycline compound is tetracycline administered in an amount which results in a serum concentration which is 0.5 µg/ml.

60. (new) A method according to Claim 46 or 56, wherein said antibiotic tetracycline compound is doxycycline, minocycline, tetracycline, oxytetracycline, chlortetracycline, demeclocycline or pharmaceutically acceptable salts thereof.

61. (new) A method according to Claim 60, wherein said antibiotic tetracycline compound is doxycycline.

62. (new) A method according to Claim 61, wherein said doxycycline is administered in an amount which provides a serum concentration in the range of about 0.1 to about 0.8 µg/ml.

63. (new) A method according to Claim 62, wherein said doxycycline is administered by sustained release over a 24 hour period.

64. (new) A method according to Claim 63, where said doxycycline is administered in an amount of 40 milligrams.